IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Attorney Docket No. 2006_0019A
Ryouichi HOSHINO et al.	:	**Confirmation No. 7559**
Serial No. 10/566,503	:	Group Art Unit 1618
Filed February 6, 2006	:	Examiner Nissa M. Westerberg
ORAL SUSTAINED-RELEASE TABLET	:	**Mail Stop: AMENDMENT**

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, **Ryouichi HOSHINO**, the undersigned, a citizen of Japan, residing at 386-2-1004,Marubayashi,Nogi-machi,Shimotsuga-gun,TOCHIGI 329-0111 Japan, do hereby declare:

1. That I am a co-inventor of the above-identified application.

2. That I graduated from Nihon University on March 1981 with a degree in bachelor.

3. That I work in the Chemical Process & Pharmaceutics Division of Development Research Laboratories of Clinical Development Center of Kyorin Pharmaceutical Co., Ltd., one of the assignees of the above-identified application.

4. I have consistently pursed pharmaceutical formulation study as a researcher.

OBJECT OF THE DECLARATION

The Office Action dated June 16, 2009, with regard to the above-identified U.S. Patent Application (Serial No. 10/566,503), includes an obviousness rejection based on Baichwal (U.S. Patent 5,399,359) in view of Miyachi et al. (Bioorganic & Medicinal Chemistry 1999) and Alderman (U.S. Patent No. 4,734,285).

In order to clarify the difference between the relied upon prior technology and the invention of the above-identified application, specifically, the unobviousness of the invention set forth in the above-identified application, the following experiments were conducted under my direction and control.

The Test Period for the Experiments was from October 26, 2009 to November 12, 2009.

METHODS

Pharmaceutical Formulation

Using the pharmaceutical formulation as shown in Table 1 (having the same components in the same amounts as in Example 5 described in the specification of U.S. Patent Application No. 10/566,503) as a common formulation, KRP-197 (imidafenacin) sustained-release tablets were made through a direct compression method, a dry granulation method and a wet granulation method, as exemplified in the cited prior art (Alderman, U.S. Patent No. 4,734,285). I have confirmed whether the qualities (content uniformity) of the obtained tablets made in accordance with the prior art technology are inferior to the experiment results of tablets obtained in Example 5.

Table 1: Components and contents thereof in Example 5, according to the invention of the above-identified application

Component Type	Common Name (Trade Name)	Specification	Name of Manufacturer	Content (mg)
Actice ingredient	KRP-197	Exhibit	Development Research Laboratory of Kyorin Pharmaceutical Co., Ltd.	0.5
Excipient	Partly pregelatinized starch (Starch 1500)	Japanese Pharmaceutical Excipients	Colorcon Japan, LLC	83.5
Sustained-Release Aid	Hydroxypropylmethylcellulose 2910 (Metlose 60SH-4000)	Japanese Pharmacopoeia	Shin-Etsu Chemical Co., Ltd.	80
Lubricant	Magnesium stearate (vegetable magnesium stearate)	Japanese Pharmacopoeia	Nitto Kasei Kogyo K.K.	1

Preparation of KRP-197 (imidafenacin) sustained-release tablets through various methods

1. Direct compression method

9 g of partly pregelatinized starch was added to 1 g of KRP-197 (imidafenacin) in a high speed mixer/kneader (Mechanomill Type MM -10N, product of Okada Seiko Co., Ltd.) and mixed for 5 minutes at 500 rpm to prepare KRP-197 (imidafenacin) of the tenth trituration. 90 g of partly pregelatinized starch was added to 10 g of KRP-197 (imidafenacin) of the tenth trituration in a high speed mixer/kneader and mixed for 5 minutes at 500 rpm to prepare KRP-197 (imidafenacin) of the hundredth trituration. 68 g of partly pregelatinized starch and 160 g of hydroxypropylmethylcellulose 2910 were added to 100 g of KRP-197 (imidafenacin) of the hundredth trituration in a mixer (V-type mixer Type 15L, product of Nihon Yakugyo Kikai K.K.) and mixed for 10 minutes at 31 rpm. 2 g of magnesium stearate was added to the mixture, and mixed for 1 minute to prepare a powdered mixture for direct compression method. The powdered mixture was compressed into tablets using a tablet compression machine (Rotary tablet compression machine HT-AP18-SSII, product of Hata Iron Works Co., Ltd.) at 40 rpm to make tablets with a diameter of 7.5 mm and a weight of 165 mg.

2. *Dry granulation method*

9 g of partly pre gelatinized starch was added to 1 g of KRP-197 (imidafenacin) in a high speed mixer/kneader (Mechanomill Type MM-10N, product of Okada Seiko Co., Ltd.) and mixed for 5 minutes at 500 rpm to prepare KRP-197 (imidafenacin) of the tenth trituration. 90 g of partly pregelatinized starch was added to 10 g of KRP-197 (imidafenacin) of the tenth trituration in a high speed mixer/kneader and mixed for 5 minutes at 500 rpm to prepare KRP-197 (imidafenacin) of the hundredth trituration. 68 g of partly pregelatinized starch and 160 g of hydroxypropylmethylcellulose 2910 were added to 100 g of KRP-197 (imidafenacin) of the hundredth trituration in a mixer (V-type mixer Type 15L, product of Nihon Yakugyo Kikai K.K.) and mixed for 10 minutes. Then, the mixture was compression-molded into a thin plate (flake) using a roller type dry compression molder (Roller Compactor Type TF-MINI, product of Freund). The obtained flake was crashed by a dry granulator (Roll Granulator Type GRN-T-54-S, product of Nihon Granulator K.K.) to form granules. 303 g of the obtained granules and 1.85 g of magnesium stearate were charged in a mixer (V-type mixer Type 15L, product of Nihon Yakugyo Kikai KK) and mixed for 1 minute at 31 rpm. The powdered mixture was compressed into tablets using a tablet compression machine (Rotary tablet compression machine HT-AP18-SSII, product of Hata Iron Works Co., Ltd.) at 40 rpm to make tablets with a diameter of 7.5 mm and a weight of 165 mg.

3. *Wet granulation method*

1 g of KRP-197 (imidafenacin), 167 g of partly pregelatinized starch and 160 g of hydroxypropylmethylcellulose 2910 were charged in a high speed mixer/granulator (High Speed Mixer LFS-GA-2J, product of Fukae Powtec) and mixed under conditions with an agitator at 100 rpm and a chopper at 1000 rpm for 5 minutes. Then, 145.66 g of ethanol (95) was added thereto and the mixture was granulated under conditions with an agitator at 250 rpm and a chopper at 2000 rpm for 4.5 minutes. The obtained granules were dried with a drier (Air Flowing Dryer Type 30C, product of Fuji Paudal Co., Ltd.) at 50°C for one hour. The dried product was sieved by 850 μm-mesh sieve. The dried product remaining on this sieve was sized by a sizer (Comil Type 197S, product of Powlex Co., Ltd.) with a screen having holes with a diameter of 1.143

mm. 302 g of the granules obtained through sieving and sizing and 1.84 g of magnesium stearate were charged in a mixer (V-type mixer Type 15L, product of Nihon Yakugyo Kikai K.K.) and mixed for 1 minute at 31 rpm to produce the powdered mixture for wet granulation with compression. The powdered mixture was compressed into tablets using a tablet compression machine (Rotary tablet compression machine HT-AP18·SSII, product of Hata Iron Works Co., Ltd) at 40 rpm to make tablets with a diameter of 7.5 mm and a weight of 165 mg.

QUALITY TEST

As to the content uniformity test and dissolution test, KRP-197 (imidafenacin) was quantified by liquid chromatography. Table 3 shows the used measurement instruments.

Table 2: Measurement Instruments

Test	Name	Type	Name of Manufacturer
Content uniformity test	Liquid chromatograph	Alliance System available from Waters	Waters
Dissolution test	Dissolution tester	SR8-Plus	Hanson
	Liquid chromatograph	Alliance System available from Waters	Waters

RESULTS

Content uniformity test

As shown in Table 3, the content uniformity of the tablets prepared in accordance with the prior art direct compression method, dry granulation method and wet granulation method were poor because of remarkable variations. In contrast to the prior art results, the content uniformity of the tablets prepared in accordance with the technique described in Example 5 of the above-identified application was favorable.

For reference, the content uniformities of other tablets are also shown in Table 3. These tablets were prepared in accordance with the techniques described in Example 4 and Example 6

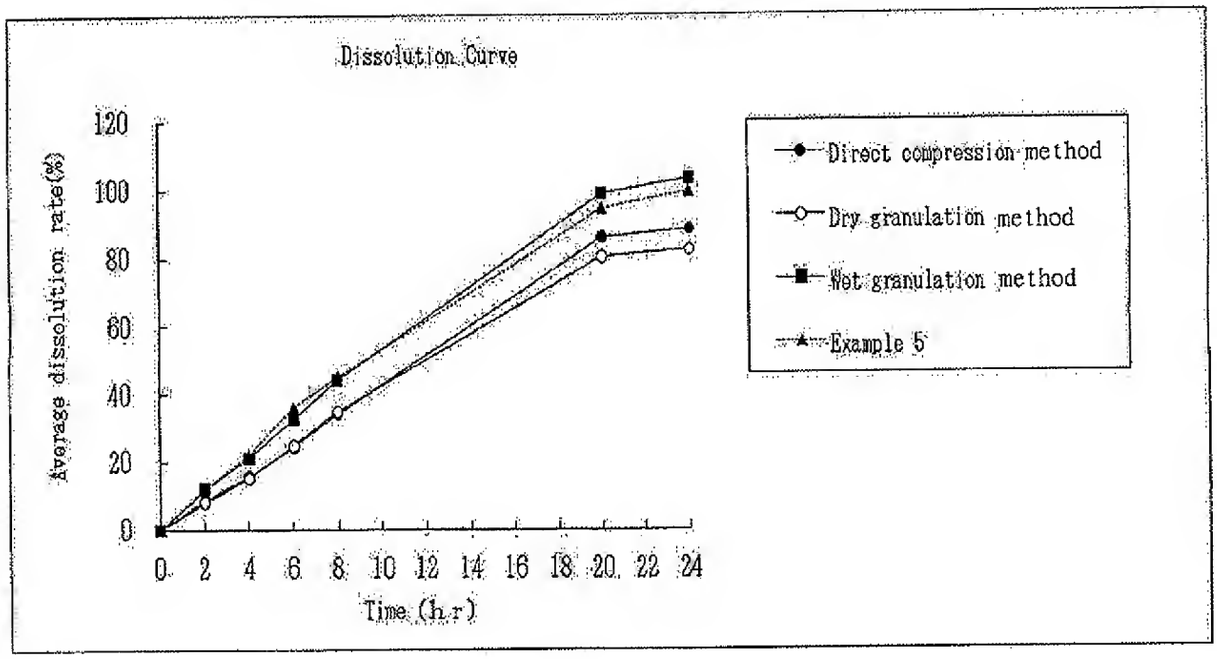
of the above-identified application, wherein the amount of hydroxypropylmethylcellulose was changed in order to control the release of KRP-197 (imidafenacin). The results were favorable as in Example 5. Accordingly, it has been confirmed that the invention of the above-identified application provides superior content uniformity of sustained release tablets containing a small amount of KRP-197 (imidafenacin).

Table 3: Content uniformity test

Technique/Method		Prior Art (Alderman, US Patent No. 4,734,285)			Present Invention (USSN 10/566,503)		
		Direct compression method	Dry granulation method	Wet granulation method	Example 5	Example 4 (reference)	Example 6 (reference)
Content of active ingredient		0.5mg	0.5mg	0.5mg	0.5mg	0.5mg	0.5mg
Content of hydroxypropylmethylcellulose (%)		48	48	48	48	24	73
Content of each tablet	1	80.3	84.0	109.7	100.2	98.4	99.6
	2	86.8	83.0	98.7	100.3	98.0	96.4
	3	86.4	83.3	112.9	100.4	97.2	98.3
	4	85.5	87.0	109.6	97.7	98.4	98.6
	5	108.3	84.2	100.0	102.1	97.4	95.2
	6	96.5	112.5	96.7	98.4	99.2	96.2
	7	100.7	83.9	100.2	99.8	97.2	98.5
	8	137.4	89.0	115.7	96.5	96.9	98.9
	9	86.4	87.5	106.5	98.9	99.2	98.9
	10	86.2	90.0	98.8	97.8	96.4	94.5
Average (mg)		95.5	88.4	104.9	99.2	97.8	97.5
Range (mg)		57.1	29.5	19.0	5.6	2.8	5.1
Standard deviation		17.02	8.81	6.81	1.65	0.96	1.78
Relative standard deviation		0.18	0.10	0.06	0.02	0.01	0.02

Dissolution test

As shown in the following diagram, it has been confirmed that the tablets prepared in accordance with the prior art direct compression method, dry granulation method and wet granulation method have the same function for controlling the release of KRP-197 (imidafenacin) as in Example 5 of the invention of the above-identified application.



CONCLUSION

It has been confirmed that although the tablets that contain 0.5 mg of KRP-197 (imidafenacin) and are made in accordance with the prior art technology (cited in the Office Action of June 16, 2009) can provide the function for controlling the release of drugs, they have remarkably poor content uniformity, which is the significant problem in quality.

In contrast to this result, the tablets made in accordance with the technology of the invention of the above-identified application show the favorable content uniformity in all of the examples.

Accordingly, it is clear that the present invention of the subject application is quite different from the prior art technology.

I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Ryouichi Hoshino
Ryouichi HOSHINO

December 8, 2009
Date